Quantitative value of ER, PR and Ki-67 as predictor neoadjuvant chemotherapy in LABC Luminal A and B/HER-2 negative at Ulin Hospital

Valor cuantitativo de ER, PR y Ki-67 como quimioterapia neoadyuvante predictiva en LABC Luminal A y B/HER-2 negativo en el Hospital de Ulin

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Abstract

The expression of biomarkers in breast cancer has been widely used as a prognostic and predictive indicator of hormonal therapy and chemotherapy. Currently, the biomarkers most often used as prognostic and predictive indicators for chemotherapy therapy are Estrogen receptor (ER), Progesterone receptor (PR) and proliferation of ki67. The aim of this study was to see whether the quantitative values of ER, PR, and Ki-67 could be predictors of response to anthracycline-based neoadjuvant chemotherapy (NACT) in Locally Advance Breast Cancer (LABC) luminal A and B/ HER-2 negative subtype at Ulin Hospital, Banjarmasin. To that aim, a non-random consecutively sampling method is utilized. The total sample collected was 268 patients and after going through the inclusion and exclusion criteria we obtained 83 patients that met the criteria. Given the results, our study obtained significant results of value Ki-67 as a predictor of response to anthracycline-based neoadjuvant chemotherapy (p value: 0.005 and p value PR: 0.009). Whereas ER (p value: 0.248) and PR (p value: 0.503) were not predictors of chemotherapy response. Quantitative Ki-67 values are used as a predictor of response to anthracycline-based NACT in LABC Luminal A and B/Her2 negative subtype patients.

Keyword: LABC, ER, PR, Ki-67, NACT, Anthracycline

Resumen

La expresión de biomarcadores en el cáncer de mama se ha utilizado ampliamente como indicador pronóstico y predictivo de la terapia hormonal y la quimioterapia. Actualmente, los biomarcadores más utilizados como indicadores pronósticos y predictivos de la terapia de quimioterapia son el receptor de estrógeno (RE), el receptor de progesterona (PR) y la proliferación de ki67. El objetivo de este estudio fue ver si los valores cuantitativos de ER, PR y Ki-67 podrían ser predictores de la respuesta a la quimioterapia neoadyuvante basada en antraciclina (NACT) en el cáncer de mama localmente avanzado (LABC) luminal A y B/HER- 2 subtipo negativo en el Hospital Ulin, Banjarmasin. Para ello se utiliza un método de muestreo consecutivo no aleatorio. La muestra total recolectada fue de 268 pacientes y luego de pasar por los criterios de inclusión y exclusión obtuvimos 83 pacientes que cumplieron con los criterios. Dados los resultados, nuestro estudio obtuvo resultados significativos del valor del Ki-67 como predictor de respuesta a la quimioterapia neoadyuvante basada en antraciclinas (valor de p: 0,005 y valor de p PR: 0,009). Mientras que ER (valor de p: 0,248) y PR (valor de p: 0,503) no fueron predictores de respuesta a la quimioterapia. Los valores cuantitativos de Ki-67 se utilizan como predictor de respuesta a NACT basado en antraciclina en pacientes de subtipo LABC Luminal A y B/Her2 negativo.

Palabra clave: LABC, ER, PR, Ki-67, NACT, antraciclina

Introduction

Breast cancer is one of the highest causes of death in the world in cases of malignancy. Based on GLOBOCAN 2020 data, breast cancer is the most common cancer in the world as well as in Indonesia[1,2]. In 2020, Indonesia will be one of the countries with the highest incidence of breast cancer with an incidence 30.8%. Breast cancer also reaches 16.6% of all types of cancer in Indonesia without separating gender with the highest mortality rate (15.3%)[2].

The characteristics of breast cancer patients in South Kalimantan are dominated by locally advanced breast cancer (LABC) patients. Narisuari and Manuaba at Sanglah Hospital reported that from 64 samples, 41 respondents (64.06%) had stage III breast cancer[3]. Based on PERABOI guidelines 2023 which states that around 60-70% of breast cancer patients are already in an advanced stage (stage III-IV) when they search for treatment[4].

The expression of biomarkers in breast cancer has been widely used as a prognostic and predictive indicator of hormonal therapy and chemotherapy. Currently, the most often biomarkers used are Estrogen receptor (ER), Progesterone receptor (PR) and proliferation of Ki-67[5]. In this study, we wanted to see whether quantitavie value of hormone receptor and Ki-67 could be predictors of anthracycline-based neoadjuvant chemotherapy (NACT) in LABC Luminal A and B/Her-2 negative at Ulin Hospital, Banjarmasin.

Materials and methods

This study is a retrospective cohort with the primary data source taken from the medical records of all LABC patients with Luminal Subtypes A and B/HER-2 (-) at the Ulin Hospital, Banjarmasin from 2020 - 2023 using a non-random consecutively sampling method. The total sample collected was 268 patients and after going through the inclusion and exclusion criteria we obtained 83 patients that met the criteria showed in table 1.

Inclusion criteria are patients with LABC, patients have immunohistochemistry examination results such as ER, PR, HER-2, and Ki67 obtained from the Anatomic Pathology laboratory, given 4 times NACT (FAC, FEC, AC or EC), has data such as physical examination (tumor size before and after chemotherapy), tumor histopathology, and immunohistochemistry, the patient agrees to be a sample by signing an informed consent.

The exclusion criteria in this study were patients who died or had serious chemotherapy side effects (severe cardiotoxicity and bone marrow dysplasia), incomplete NACT or patients who underwent NACT 5 times or more, patients with HER-2 (+). Data analysis consisted of descriptive analysis and multinomial regression test to determine the relationship between quantitative values of ER, PR and Ki-67 on the response to anthracycline-based NACT in LABC Luminal A and B/HER-2 (-) subtypes.

Table 1. Patient characteristics.

Characteristic	Average	Total (n=83)	Presentase (%)
Age			
< 50 years	44 (27-49)		
50-65 years	56 (50-63)	40	48,2
> 65 years	66 (65-84)	35	41,2
Mean ± SD	50.9 ± 10.8	8	9,6
Median (Min-Max)	50.0 (27.0 – 84.0)		
Subtype			
Luminal A		38	45,8
Luminal B/HER-2		45	54,2
Negative			
Tumor Size			
< 5 cm		3	3,6
≥ 5 cm		80	96,4
Nodule			
N0-1		55	66,3
N2-3		28	33,7

Results

In Table 2 can be seen that ER receptors in both ≤10% and >10% categories, majority had a partial response response to chemotherapy. The same thing can be seen at PR receptors in both the ≤20% and >20% categories, the majority of had a partial response. Then, Ki67 value ≤20%, the majority had a partial response chemotherapy, while in the Ki67 value >20% the majority had a partial and complete chemotherapy response with a percentage of around 45.5% each.

The results show that the ER p value for complete response and partial response is 0.516 and 0.479. Meanwhile, the PR p value for complete response and partial response is 0.503 and 0.409 respectively. Ki-67 obtained a P value of 0.005 for complete response and 0.009 for partial response.

Table 2. Distribution of Estrogen Receptors, Progesterone Receptors, Ki-67 and Chemotherapy Response.

Receptor	Chemoterapy Response				Total (n=83)
	CR (n=10)	PR (n=46)	SD (n=4)	PD (n=4)	
ER					
≤10%	5 (21.7%)	15 (65.2%)	1 (4.3%)	2 (8.7%)	23 (100.0%)
>10%	21 (35.0%)	34 (56.7%)	3 (5.0%)	2 (3.3%)	60 (100.0%)
PR					
≤20%	13 (28.3%)	29 (63.0%)	3 (6.5%)	1 (2.2%)	46 (100.0%)
>20%	13 (35.1%)	20 (54.1%)	1 (2.7%)	3 (8.1%)	37 (100.0%)
Ki67					
≤20%	6 (15.4%)	29 (74.4%)	2 (5.1%)	2 (5.1%)	39 (100.0%)
>20%	20 (45.5%)	20 (45.5%)	2 (4.5%)	2 (4.5%)	44 (100.0%)

CR= Complete Response, PR = Partial Response, SD = Stable Disease, PD = Progresive Disease

Discussion

In statistical tests, results were obtained where the quantitative values of ER and PR could not be used as predictors of response to anthracycline-based NACT in patients with LABC Luminal A and B/Her-2 negative subtype. These results are in accordance with research conducted by Tan et al. which stated that the hormonal receptor (HR) values, both ER and PR, did not have significant results as predictors of chemotherapy, but the ER value could be a patient prognostic factor[6]. This is also supported by research conducted by Prihantono and Faruk which states that currently there are no indicators that can accurately predict the response to breast cancer chemotherapy[7].

We found that ER could not be a predictor factor because many of the LABC patients treated at the Surgical Oncology Outpatient Department at Ulin Banjarmasin Regional Hospital came with large tumor sizes. Which in this condition it will be difficult to achieve a complete clinical response. However, ER-positive patients have a better prognosis because this group will achieve relapse-free survival (RFS) if they receive endocrine therapy compared to patients who do not receive endocrine therapy[6] (Figure 1).

This is supported by research conducted by Lumachi et al. which states that in breast cancer patients with ER (+), endocrine therapy has several benefits, including prolonging disease-free survival (DFS) and overall survival (OS), and reducing the risk of recurrence both in early and advance breast cancer[8]. Stamatovic et al. obtained the results of breast cancer patients with ER (-) and HER-2 (+) significantly experiencing pathological complete response (pCR) but there was no difference in DFS and OS between the 4 breast cancer subtypes[9]. Tan et al. stated only few research about the predictive or prognostic value of changes in receptor status. Several studies have shown a correlation between hormone receptor (HR) conversion and treatment response but cannot be concluded because there is still some controversy[6].

In contrast, Tacca et al. and Hirata et al. observed that there was no significant difference in PFS and OS rates between endocrine therapy administered to HR-negative and HR-positive patients before and after NACT but both indicated that a change in HR status from negative to positive could be an indicator for better outcome[10,11].

Perez-Garcia et al. stated that in a group of breast cancer patients receiving NACT, PR status independently predicted pCR in the entire population as well as in the group treated with anthraskilines + taxanes and in the HER-2(+) subgroup[12]. Other studies related to PR

status as a predictor did not obtain satisfactory results because PR was not studied independently. PR is very closely related to ER, as research from Osako et al. in multivariate analysis, negative ER or negative PgR expression was a significant predictive factor for achieving pCR[13].

An important result from our study is that the Ki-67 value can be a predictor factor in assessing the response to anthracycline-based NACT in LABC luminal A and B HER-2 Negative subtypes. In the Ki-67 ≤ 20% group, 6 patients (15.4%) experienced a complete response and 29 patients (74.4%) experienced a clinical partial response, while in the Ki-67 > 20% group there were 20 patients (45.5%) who experienced a clinical complete response and 20 patients (45.5%) experienced a clinical partial response.

The results of this study are supported by previous research by Kim et al. which states Ki-67 expression in breast cancer tissue may be an effective factor for predicting response to neoadjuvant chemotherapy. It was also found that if Ki-67 expression was 25% or more, it would be better in predicting chemotherapy response. In addition, Ki-67 is a useful predictive factor for pCR, especially in patients with ER (–) and HER-2 (+) breast cancer[14].

Other research conducted by Mukai et al. obtained strong correlation results between the level of reduction in Ki-67 values and the level of pCR, as well as between the reduction in tumor size and the level of pCR[15]. Devi et al. assessing changes in expression of Ki-67 values before and after NACT revealed that the group with a decrease in Ki-67 value >12.5% correlated significantly with good clinical response[16].

Researchers found that tumors with higher levels of cell proliferation responded better to chemotherapy than tumors with lower levels of proliferation. Ki-67 is widely known as a proliferation marker and many studies show a positive correlation between Ki-67 expression and the proliferative cell fraction in tumors. Therefore, many researchers have investigated the relationship between Ki-67 expression and chemotherapy response in breast cancer patients, where high Ki-67 expression has been shown to provide a better response to chemotherapy[17].

However, until now there is still debate as to best cut-off value for Ki-67 expression that more accurate in predicting chemotherapy response. As in several studies that have been conducted, Nishimura stated that 12% is the appropriate cut-off as the median of the Ki-6718 expression value. Li et al. used a value of 20% as a cut-off to differentiate low and high Ki-67 expression[18,19]. Finally from Kim et al. which used a value of 25% as a meaningful cut-off value[14]. Based on the 2023 PERABOI guidelines, we used 20% as a cut-off value to differentiate between high and low proliferation Ki-67[4].

Although all the above studies prove that high Ki-67 expression is a predictive factor for pCR, it is important to establish a standard measurement system and rational criteria for a cut-off value of Ki-67 expression that is capable being a predictor of response to NACT in LABC patients. Researchers suggest that further research be carried out with the latest methodology to determine rational cutoff value for Ki-67 expression and it is hoped that the results of this study will be useful and can also be validated in multicenter studies which will contribute to the establishment of rational criteria for determining Ki-67 expression.

Figure 1. Ki-67 Multinomial Logistic Regression Test results for (a.) complete response and (b.) partial response.

a.

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B) Lower	Upper
Step 1[a]	Ki67	-1.522	.537	8.030	1	.005	.218	.076	.625
	Constant	1.705	.444	14.754	1	.000	5.500		

a. Variable(s) entered on step 1: Ki67.

b.

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B) Lower	Upper
Step 1[a]	Ki67	1.247	.476	6.876	1	.009	3.480	1.370	8.838
	Constant	-1.065	.367	8.429	1	.004	.345		

a. Variable(s) entered on step 1: Ki67.

Conclusions

The quantitative value of Ki-67 can be used as a predictor of response to anthracycline-based NACT in LABC luminal A and B/ HER-2 negative subtype at Ulin Hospital Banjarmasin, both in complete response and partial response. Meanwhile, the quantitative values of ER and PR were not significant as predictors of response to anthracycline-based neoadjuvant chemotherapy in LABC.

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